CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205394Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA, 505(b)(2) resubmission
Application Number(s)	205394
Priority or Standard	Standard
Submit Date(s)	09/29/2018
Received Date(s)	09/29/2018
PDUFA Goal Date	03/29/2019
Division/Office	Division of Neurology Products/Office of New Drugs
Reviewer Name(s)	Laura Jawidzik, MD
Review Completion Date	12/27/2018
Established/Proper Name	Rizatriptan
(Proposed) Trade Name	Rizaport
Applicant	IntelGenx Corporation
Dosage Form(s)	Oral film
Applicant Proposed Dosing Regimen(s)	Single dose of 10mg
Applicant Proposed Indication(s)/Population(s)	Treatment of acute migraine in adults and pediatric patients age 12 and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of acute migraine in adults and pediatric patients age 12 and older

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Rizaport, also known as rizatriptan oral film, is a serotonin receptor agonist belonging to the class of drugs known as triptans. Rizaport is an immediate release oral film formulation. Rizatriptan is indicated for the acute treatment of migraine with or without aura in adults and pediatric patients age 6 and older.

Rizatriptan is an approved product that comes in several formulations including a tablet and an orally dissolving tablet. Rizatriptan is also available in generic form as a tablet and an orally dissolving tablet. Both generic dosage forms are available in 5mg and 10mg strengths. The applicant previously submitted a 505(b)(2) application for this new formulation of rizatriptan. The prior application for Rizaport received a complete response in 2014 because of numerous deficiencies from the Chemistry, Manufacturing, and Controls (CMC) discipline. Previously the (b) (4) The applicant (b) (4) is seeking approval of only the 10mg dose.

The listed drug is Merck's product, Maxalt-MLT under NDA 020865. Maxalt-MLT is approved for acute treatment of migraine in adults and pediatric patients age 6 and older. The adult recommended dosage of Maxalt-MLT is 5mg or 10mg as a single dose with repeat doses separated by at least 2 hours. Maximum recommended dose in 24 hours is 30mg. In pediatric patients, 5mg single doses are recommended in patients less than 40kg, and 10mg single doses in patients weighing 40kg or more. For business reasons, Merck is no longer marketing the 5mg dose of Maxalt and Maxalt-MLT although the 5mg dose continues to be available in a generic. The 5mg dose is considered a safe and effective dose of rizatriptan.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This is a 505(b)(2) application which utilized a bioequivalence study to bridge the efficacy and safety of the product to Maxalt. The Office of Clinical Pharmacology has reviewed the results of the pivotal bioequivalence study and concluded that Rizaport is bioequivalent to Maxalt.

1.3. Benefit-Risk Assessment

The overall risk benefit assessment of Rizaport is acceptable. Rizatriptan has been marketed in the United States for adult migraine patients since 1998 and has a well-characterized safety profile. No new adverse events were discovered in the course of the development program for Rizaport that would affect the risk benefit assessment.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
x	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Migraine is a very common, chronic neurological disease with a broad spectrum of frequency and severity. Migraine can be a serious and, at times, disabling condition that can impact the quality of patients' lives.

Migraine is a disease characterized by recurrent attacks of headache that are typically moderate to severe in intensity. The attacks tend to be unilateral headaches associated with symptoms such as nausea, vomiting, phonophobia, or photophobia. A typical migraine can be exacerbated by even minor physical activity and may last from 4 to 72 hours. Some patients may experience an aura 30 minutes to an hour prior to the onset of their headache, and other patients may experience a general prodrome a day or two prior to the onset of the headache.

2.2. Analysis of Current Treatment Options

There are many FDA-approved therapies for the treatment of acute migraine, and many others that are used off-label. In 2015, the American Headache Society (AHS) published a guideline on the treatment of acute migraine therapies (Marmura et al. 2015).

The guideline lists the following drugs as having Level A evidence (established as effective): acetaminophen, acetylsalicylic acid, diclofenac, ibuprofen, naproxen, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, dihydroergotamine (intranasal and pulmonary inhaler), and butorphanol. The following combination products are considered to have Level A evidence as well: sumatriptan/naproxen, and acetaminophen/acetylsalicylic acid/caffeine.

The following drugs and combination products are considered by this guideline to have Level B evidence (probably effective): chlorpromazine, droperidol, metoclopramide, prochlorperazine, flurbiprofen, keoprofen, ketorolac, IV magnesium, isometheptene, dihydroergotamine (SC, IV, IM); ergotamine/caffeine; tramadol/acetaminophen; and codeine/acetaminophen.

The following drugs and combination products are considered by this guideline to have Level C evidence (possibly effective): valproate (IV), phenazone, codeine, ergotamine, butorphanol (IM), meperidine, methadone, tramadol, dexamethasone, lidocaine (intranasal); butalbital/acetaminophen/caffeine, and butalbital/acetaminophen/caffeine/codeine.

3. Regulatory Background

The IND number associated with Rizaport is 110753. The IND was never formally opened with a clinical study. A pre-investigational new drug (IND) meeting was held for rizatriptan oral film on February 23, 2011. This meeting addressed the applicant's plans for establishing bioequivalence to Maxalt-MLT and CMC related issues.

A Type B pre-NDA meeting was held on November 7, 2012. This meeting primarily focused on CMC related issues, and the applicant's plan for submitting a 505(b)(2) application. The Division informed the applicant that the product triggers PREA because it is a new dosage form. The applicant was instructed to provide a plan for addressing each pediatric age group (age 0 to 6 years, 6 to 11 years, and 12 to 17 years). Merck received Hatch-Waxman Exclusivity for Maxalt for studies in pediatric patients age 6-17 that was due to expire in 2015. The applicant was advised to take this information in consideration when planning the timeline for PREA required studies.

The applicant submitted a 505(b)(2) NDA on March 26, 2013. The application was filed with a goal date of February 3, 2014. The filing letter outlined several CMC-related potential review issues and alerted the applicant that a Pediatric Plan was required. Per the filing letter, "We note that you have not fully addressed how you plan to fulfill this requirement. While we acknowledge the rationale behind your requested deferral of pediatric studies, this proposal is inadequate at this time. As noted above, a Pediatric Plan outlining your planned pediatric studies is a required component of your application. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication(s) proposed in this application."

On July 9, 2013, the sponsor submitted a waiver request to the NDA for pediatric studies with a very minimal outline of a Pediatric Plan and the intent to leverage Maxalt's data after the expiration of pediatric exclusivity in 2015.

PeRC meeting recommendations from December 4, 2013 stated the following: "Once exclusivity has expired for Maxalt, the sponsor may satisfy their PREA requirement by submitting reference to the full pediatric labeling for Maxalt."

A Complete Response (CR) was issued January 31, 2014. It was understood that the PREA requirements could be fulfilled once the pediatric exclusivity for Maxalt expired.

Following the CR, a Type A End-of-Review meeting was held on March 12, 2014, to discuss the deficiencies. The applicant responded to the original CR in February 2014; however, an Acknowledge Incomplete Response letter was issued on April 10, 2014, as the applicant did not fully address all aspects of the CR. Another End-of-Review meeting was held August 7, 2014, where the primary discussion was related to CMC issues.

The applicant submitted another incomplete response in October 2017 and in November 2017 another Acknowledge Incomplete Response letter was issued to the applicant. In that letter, the Division recommended to the applicant to conduct another relative BA study using the final proposed to-be-marketed drug product as the overall CMC changes were substantial changes that could potentially impact in vivo performance. The Division also recommended the applicant request a Type C meeting specifically to address CMC-related issues. The CMC Type C meeting was held March 22, 2018, via teleconference.

The current resubmission was received September 29, 2018 (eCTD sequence 0005). The sponsor submitted a comparative bioavailability study of Rizaport to Maxalt-MLT. The sponsor submitted (b) (4) .

Reviewer's comment: The sponsor's request (b) (4) *is not justified. The sponsor will need to address this population to satisfy PREA requirements in the pediatric population. The sponsor will need to develop* (b) (4) *dose for patients weighing under 40kg.*

4. Sources of Clinical Data and Review Strategy

The sponsor has submitted a single clinical study with the application, study BPSI 2259. The study will be reviewed for safety. No efficacy studies were submitted.

5. Review of Relevant Individual Trials Used to Support Safety

Study BSPI 2259

Title

A Single-Dose, Randomized, Open-Label, Three-Way Crossover, Pivotal Comparative Bioavailability Study of Rizatriptan 10mg Oral Films, Maxalt-MLT 10mg Orally Disintegrating Tablets, and Maxalt Lingua 10mg Oro-Dispersible Tablets in Healthy Male and Female Volunteers under Fasting Conditions

Overview and Objective

To assess the comparative bioavailability of Rizaport 10mg oral film, Maxalt-MLT 10mg orally disintegrating tablets, and Maxalt Lingua 10mg oro-dispersible tablets. To assess the safety and tolerability of Rizaport in healthy, non-smoking male and female volunteers under fasting conditions.

Trial Design

This was a single dose, randomized, open-label, three-way crossover, three-period, three-sequence, three-treatment, comparative bioavailability study. The drug administrations were separated by a wash-out of three calendar days.

Subjects were randomized equally into one of the following three sequences:

	Period 1	Period 2	Period 3
Sequence 1	A	B	C
Sequence 2	B	C	A
Sequence 3	C	A	B

A: Rizaport 10mg oral film
B: Maxalt-MLT 10mg orally disintegrating tablets (U.S. reference product)
C: Maxalt Lingua 10mg oro-dispersible tablet (European reference product)

Safety was evaluated through assessment of adverse events, laboratory evaluations, vital signs, and ECGs.

Table 1 Study Schedule of Events

Procedure/Activity	Time points				
	Screening	Period 1	Period 2	Period 3	Post-Study
Study ICF	X				
Medical History	X				
BMI	X				
ECG	X	X[h]	X[h]	X[h]	X
Vital Signs (BP, HR, RR and temperature)	X				X
Physical Exam	X				X
Laboratory Testing	X				X
Drugs of Abuse	X	X[a]	X[a]	X[a]	
Breath Alcohol Test	X	X[a]	X[a]	X[a]	
Urine Cotinine	X	X[a]	X[a]	X[a]	
Pregnancy Test[#]	X	X[a]	X[a]	X[a]	
Inclusion/Exclusion Assessment	X				
Vital Signs (BP & HR)		X[b]	X[b]	X[b]	
Restrictions Compliance Check		X[c]	X[c]	X[c]	
Study Drug Administration		X	X	X	
PK Blood Sampling		X[d]	X[d]	X[d]	
Adverse Event Reporting		X[e]	X[e]	X[e]	X
Meals		X[f]	X[f]	X[f]	
Visual Inspection of the buccal cavity		X[g]	X[g]	X[g]	

[#]- Serum pregnancy at screening and Urine pregnancy at check-in.
[a]- At check-in only.
[b]- Vital signs measurements (BP and HR) were obtained at pre-dose and at 2, 4 and 12 hours after dosing in each study period.
[c]- Confirmed at check-in and each ambulatory blood draw, if applicable.
[d]- PK sampling - Pre-dose (0) and at 0.083, 0.167, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 4, 6, 8 and 12 hours after dosing in each study period.
[e]- Pre-dose conditions at Period 1 check-in and confirmed at each check-in and each ambulatory blood draw, if applicable.
[f]- Meals were served at check-in and approximately at 4.5 and 9.5 hours after dosing.
[g]- At 10 minutes and 1 hour after dosing in each study period.
[h]- At approximately 2.5 hours after dosing in each study period.

This table is taken from the study report body from BPSI 2259

Findings

Initially 30 subjects were randomized with 10 subjects in each sequence. Two subjects were dismissed from sequence 1 and two subjects did not complete sequence 3.

Table 2 Demographics of the Subjects Completing the Study

	Age (years)	Height		Weight		BMI	Race/Ethnicity	
		(cm)	(in)	(kg)	(lb)			
Mean	31	169.6	66.8	73.3	161.7	25.5	**White**	4
+/- SD	5	9.3	3.7	10.1	22.2	2.8	**Black**	12
Median	33	170.4	67.1	72.6	160.1	25.4	**Asian**	5
							Native	0
Range	19-40	146.3-183.6	57.6-72.3	56.7-97.5	125.0-214.9	20.7-29.7	**Hispanic/ Latino**	5

Sponsor's table from the report body for study BPSI-2259

6. Review of Safety

In study BSPI 2259, 26 subjects were exposed to single doses of Rizaport oral film.

6.1. Safety Results

6.1.1. Deaths

None.

6.1.2. Serious Adverse Events

None.

6.1.3. Dropouts and/or Discontinuations Due to Adverse Effects

One subject withdrew due to an adverse event listed as vessel puncture site pain.

6.1.4. Significant Adverse Events

None.

6.1.5. Treatment Emergent Adverse Events and Adverse Reactions

For each subject, the buccal cavity was visually inspected 10 minutes and 1 hour after administration of the oral film for full disappearance of the soluble film and any mucosal irritation. No mucosal irritation was reported for any subject. For subjects receiving Rizaport, the most common AE was headache in 2 subjects. AEs experienced by only one subject each

were the following: headache, dizziness, fatigue, nausea, and neck pain. All AEs were reported as mild.

Reviewer's comment: No new safety signals were identified. No changes to the labeling will be recommended.

6.1.6. Laboratory Findings

Prior to each study period, each subject underwent laboratory testing including hematology, chemistry, and urinalysis. There were no AEs related to laboratory findings.

6.1.7. Vital Signs

During the study there were several subjects who had AEs related to vital sign measurements. One subject experienced bradycardia, and two experienced an irregular heart rate. None of these subjects were in the Rizaport treatment group (Group A).

6.1.8. Electrocardiograms (ECGs)

An ECG was recorded at approximately 2.5 hours after dosing during the study for each of the three study periods. No clinically significant on-study ECG assessments were reported during this study.

7. Labeling Recommendations

7.1. Prescription Drug Labeling

This is a 505(b)(2) application. The applicant is relying on the findings of safety and efficacy of Maxalt-MLT (NDA 020865). The label will be consistent with the prescribing information for FDA-approved label for Maxalt-MLT except for the pediatric prescribing information and other information pertaining to the 5mg dose. The sponsor has only developed a 10mg dose but has not developed a 5mg dose.

7.2 Nonprescription Drug Labeling

N/A

8. Postmarketing Requirements and Commitments

The sponsor will be issued a PMR for the fulfillment of the PREA requirements for pediatric patients age 6 through 11. The sponsor can fulfill the PREA requirements with the existing pediatric labeling from Maxalt, but they will need to develop an appropriate pediatric formulation.

9. Appendices

9.1. References

N/A

9.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): BPSI 2259

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S		

Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAURA A JAWIDZIK
03/27/2019 03:09:54 PM

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07/07/2019 07:32:56 AM

CLINICAL REVIEW

Application Type	NDA, 505(b)(2)
Application Number(s)	205394
Priority or Standard	Standard
Submit Date(s)	03/26/13
Received Date(s)	03/27/13
PDUFA Goal Date	2/03/14
Division / Office	Division of Neurology Products
Reviewer Name(s)	Nushin Todd, MD, PhD
Review Completion Date	01/15/14
Established Name	Rizatriptan Oral Film
(Proposed) Trade Name	Rizaport
Therapeutic Class	Triptan
Applicant	RedHill Biopharma
Formulation(s)	Oral film
Dosing Regimen	(b) (4) 10 mg single dose
Indication(s)	Acute migraine
Intended Population(s)	Adult patients with migraine

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The applicant has developed an immediate release oral film formulation of rizatriptan for the treatment of acute migraine in adults. The product, Rizaport, is similar in (b) (4) dosage regimen, and route of administration as the referenced drug, Maxalt-MLT® Orally Disintegrating Tablet, marketed by Merck.

There are no clinical safety issues impeding the approval of the proposed product. There are, however, numerous deficiencies from the Chemistry, Manufacture and Controls discipline that justifies a Complete Response. It is therefore recommended that a Complete Response be issued to the applicant.

1.2 Risk Benefit Assessment

The overall risk to benefit assessment of Rizaport is acceptable. Rizatriptan, marketed in the United States for adult migraine patients since 1998, has a well characterized safety profile. According to the Clinical Pharmacology reviewer for this application, Rizaport has been shown to be bioequivalent when compared to the referenced drug, Maxalt-MLT®. Further, no new or unexpected adverse events were discovered in the course of the development program of Rizaport.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

The applicant seeks approval for Rizaport, an immediate release oral film formulation of rizatriptan, for the treatment of acute migraine in adults. The application is submitted in accordance with Section 505(b)(2) of the Food, Drug and Cosmetic Act. The reference

listed drug for this application is Merck's product, Maxalt-MLT® (rizatriptan benzoate), NDA 20865. Maxalt-MLT® was originally approved by the FDA for the treatment of acute migraine in adults on June 29, 1998, and is commercially available as 5 mg and 10 mg orally disintegrating tablets.

The clinical program that forms the basis of this application consists of one bioequivalence study conducted in 26 healthy male and female volunteers. The study compared the rate and extent of absorption of rizatriptan under fasting conditions for Maxalt-MLT® and Rizaport. The pharmacokinetic and clinical safety findings for this pivotal study are presented in this review.

2.1 Product Information

Indication: Treatment of acute migraine, with or without aura, in adults

Dosage Form/Strength: Rizatriptan oral (b) (4) and 10 mg

Proposed Dosages: (b) (4) 10 mg single dose; separate repeat doses by at least two hours; maximum dose in a 24-hour period is 30 mg

Chemical Name: *N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate

Pharmacologic Class: Selective 5-HT1B/1D receptor agonist

Molecular Weight: Mol Wt: 269.4 (free base)

Structural Formula:

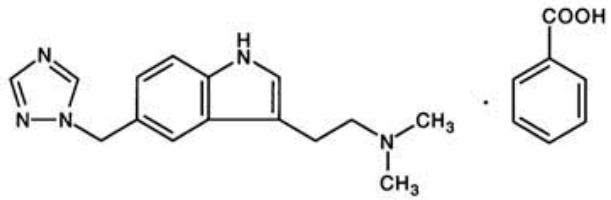


Figure 1 Structural Formula of Rizatriptan

Physical Properties: White or off-white, crystalline solid

Solubility: Soluble in water at about 42 mg/mL (expressed as free base) at 25°C

Mechanism of Action: The therapeutic activity of rizatriptan in migraine can most likely be attributed to agonist effects at 5-$HT_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release and reduced transmission in trigeminal pain pathways.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following table summarizes medications used to treat migraine. However, most are not FDA approved for a migraine indication.

Table 1 Acute Migraine Therapies in Current Use [a]

Group 1 [b]	Group 2 [c]	Group 3 [d]	Group 4 [e]	Group 5 [f]
Specific Almotriptan PO Eletriptan PO Frovatriptan PO Naratriptan PO Rizatriptan PO Sumatriptan SC, IN, PO Zolmitriptan PO, IN DHE SC, IM, IV, IN DHE IV, plus antiemetic *Nonspecific* Acetaminophen, aspirin, plus caffeine PO Aspirin PO Butorphanol IN Ibuprofen PO Naproxen sodium PO Prochlorperazine IV	Acetaminophen plus codeine PO Butalbital, aspirin, caffeine, plus codeine PO Butorphanol IM Chlorpromazine IM, IV Diclofenac K, PO Ergotamine plus caffeine plus pentobarbital plus Bellafoline PO Flurbiprofen PO Isometheptene CPD, PO Ketorolac IM Lidocaine IN Meperidine IM, IV Methadone IM Metoclopramide IV Naproxen PO Prochlorperazine IM, PR	Butalbital, aspirin, plus caffeine PO Ergotamine PO Ergotamine plus caffeine PO Metoclopramide IM, PR	Acetaminophen PO Chlorpromazine IM Granisetron IV Lidocaine IV	Dexamethasone IV Hydrocortisone IV

[a] Table modified from: Silberstein, SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55;754-762.
[b] Proven, pronounced statistical and clinical benefit (at least two double-blind, placebo-controlled studies and clinical impression of effect).
[c] Moderate statistical and clinical benefit (one double-blind, placebo-controlled study and clinical impression of effect).
[d] Statistically but not proven clinically *or* clinically but not proven statistically effective (conflicting or inconsistent evidence).
[e] Proven to be statistically or clinically ineffective (failed efficacy versus placebo).
[f] Clinical and statistical benefits unknown (insufficient evidence available).

The following are FDA approved medications used for treating migraine:

Table 2 FDA Approved Migraine Therapies in Current Use

Brand Name	Generic Name	Manufacturer	Indication
Amerge tablets	naratriptan hydrochloride	GlaxoSmithKline	acute treatment of migraine
Axert tablets	almotriptan malate	Ortho-McNeil Neurologics	acute treatment of migraine
Frova tablets	frovatriptan succinate	Endo Pharmaceuticals	acute treatment of migraine
Imitrex tablets, injection, nasal spray	sumatriptan succinate	GlaxoSmithKline	acute treatment of migraine
Maxalt tablets and Maxalt-MLT orally disintegrating tablets	rizatriptan benzoate	Merck	acute treatment of migraine
Migranal nasal spray	dihydroergotamine mesylate	Valeant	acute treatment of migraine
Relpax tablets	eletriptan hydrobromide	Pfizer	acute treatment of migraine
Sumavel DosePro injection	sumatriptan succinate	Zogenix	acute treatment of migraine
Zomig tablets. nasal spray; and Zomig-ZMT orally disintegrating tablets	zolmitriptan	AstraZeneca	acute treatment of migraine
Blocadren tablets	timolol maleate	Merck	prevention of migraine
Depakote ER tablets	divalproex sodium	Abbott Laboratories	prevention of migraine
Inderal tablets, capsules	propranolol hydrochloride	AstraZeneca	prevention of migraine
Topamax tablets, sprinkle capsules	topiramate	Ortho-McNeil Neurologics	prevention of migraine
Over-the-Counter Products			
Advil Migraine capsules	ibuprofen	Wyeth Consumer Healthcare	treatment of migraine
Excedrin Migraine tablets, caplets	acetaminophen, aspirin, caffeine	Novartis Consumer Health	treatment of migraine
Motrin Migraine Pain caplets	ibuprofen	McNeil Consumer & Specialty Pharmaceuticals	treatment of migraine

Source: Adapted from Consumer Magazine, 2006

The majority of FDA approved migraine products are the triptans, summarized in Table 3.

Table 3 Triptan Therapies Approved for Acute Migraine Treatment in the US

Trade (Generic) Name	NDA	Date of FDA Approval	Route of Delivery
IMITREX® Injection (sumatriptan)	20-080	December 12, 1992	Subcutaneous injection
IMITREX® Tablets (sumatriptan)	20-132	June 1, 1995	Tablet
IMITREX® Nasal Spray (sumatriptan)	20-626	August 26, 1997	Nasal spray
Zomig® (zolmitriptan)	20-768	November 25, 1997	Tablet
Amerge® (naratriptan)	20-763	February 10, 1998	Tablet
Maxalt® / Maxalt-MLT® (rizatriptan)	20-864 / 20-865	June 29, 1998	Tablet / orally dissolving tablet
Zomig-ZMT® (zolmitriptan)	21-231	February 13, 2001	Orally dissolving tablet
Axert® (almotriptan)	21-001	May 7, 2001	Tablet
Frova® (frovatriptan)	21-006	November 8, 2001	Tablet
Relpax® (eletriptan)	21-016	December 26, 2002	Tablet
Zomig® (zolmitriptan)	21-450	September 30, 2003	Nasal spray
Sumavel® DosePro (sumatriptan)	22-239	July 15, 2009	Subcutaneous injection

2.3 Availability of Proposed Active Ingredient in the United States

Rizatriptan is the active ingredient in Rizaport. It is the same active ingredient found in Maxalt and Maxalt-MLT. The FDA approved Maxalt and Maxalt-MLT for adult use in June 1998 (NDA 20-864 and 20-865, respectively). Rizatriptan is widely available in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

The safety profile of rizatriptan in adult patients with a clear diagnosis of migraine has been established. While generally recognized as safe and effective, there have been concerns regarding cardiac-related adverse events with triptan use. Fatalities have been reported within the triptan class due to cardiac causes. While perhaps vasospastic origin, the phenomenon remains pathologically undefined. Cerebrovascular events and fatalities have also been described, but this relationship is confounded by the presence of these complications in the migraine population in general. Other (non-coronary artery) vasospasm-type events have been described with triptan use including

peripheral vascular and colonic ischemia and (rarely) transient and permanent blindness. A precise, clear relationship of these complications to the therapy, accompanied by an understanding of the pathophysiology, remains elusive, again reflecting the confounding nature of background migraine condition. The incidence of all of these disorders remains low when the widespread use of triptans is considered.

Nevertheless because of the risk of myocardial ischemia and/or infarction and other adverse cardiac events, the rizatriptan label clearly states that it should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD). Similarly it should not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation reveals satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The current label acknowledges the sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. The conclusion is that if, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, triptans should not be administered.

Still further, in patients whose risk factors predict CAD but who have a satisfactory cardiovascular evaluation, the rizatriptan label strongly recommends that the first administration of rizatriptan take place in the setting of a physician's office or similar medically staffed and equipped facility. As a further safeguard, acknowledging cardiac ischemia can occur in the absence of clinical symptoms, the label suggests consideration be given to obtaining an electrocardiogram during the interval immediately following the first use of rizatriptan in these patients with risk factors.

The current label recommends patients who are intermittent long-term users of rizatriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use the drug. In considering this recommendation for periodic cardiovascular evaluation, it is noted that patients with cluster headache are predominantly male and over 40 years of age, which are risk factors for CAD.

The development of a potentially life-threatening serotonin syndrome may occur with triptans, including rizatriptan, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Development of Rizaport was conducted under IND 110,753. In the course of the development program, two meetings with the Division were requested by the applicant:

- Pre-IND teleconference (February 23, 2011)
- Pre-NDA teleconference (November 7, 2012)

The following is a summary of the clinical issues discussed.

Pre-IND teleconference (February 23, 2011)
Prior to the teleconference the applicant submitted an information package which included the planned development program for their product as well as questions for the Division. The applicant reported plans of developing (b) (4) 10 mg strength of rizatriptan oral film. (b) (4)

The Division concurred with the proposed clinical protocol. The Division also concurred that it was not necessary to conduct nonclinical studies to support development and approval of rizatriptan oral film unless there are CMC issues that raise a safety concern.

The applicant cancelled the planned teleconference as the preliminary response from the Division satisfactorily addressed all of the applicant's concerns.

Pre-NDA teleconference (November 7, 2012)
The applicant provided a synopsis of the bioequivalence study in the information package prior to the scheduled meeting. The Division stated that, on face, that bioequivalence was demonstrated. However, the Division also noted that the final conclusion would depend on review of the detailed raw datasets, bioanalytical method and inspection of the study.

Pediatric issues
Although the applicant did not pose any pediatric study related questions for the Pre-NDA meeting, the Division conveyed to the applicant that the product is considered a new dosage form. As such, the application will trigger the Pediatric Research Equity Act (PREA). The applicant would therefore need to submit a Pediatric Study Plan.

During the pre-NDA meeting, it was discussed that pediatric exclusivity for Maxalt is due to expire on June 15, 2015. The applicant was advised to consider the protected pediatric information that appears in Maxalt labeling and the ability to leverage this existing data when the pediatric exclusivity expires when planning the timeline for PREA required studies.

On December 4, 2013, the Pediatric Review Committee (PeRC) reviewed the applicant's partial waiver/deferral plan for pediatric studies. The PeRC agreed with the Division's recommendation to grant a partial waiver in pediatric patients 0 to 5 years of age because studies in this age group are impossible or highly impractical. The PeRC also noted that required pediatric studies for the reference listed drug, Maxalt, have been completed and labeling is present for Maxalt. However, this information is protected because of pediatric exclusivity. Therefore, this information cannot appear in Rizaport labeling until the pediatric exclusivity has expired. Once exclusivity has expired for Maxalt, the applicant may satisfy their PREA requirement by submitting reference to the full pediatric labeling for Maxalt.

As noted above, the Division agrees with the application's approach to rely on the Maxalt label for the PREA requirements once the pediatric exclusivity for Maxalt expires. However, despite the acceptability of this approach, the Complete Response letter, as a regulatory requirement, must include a PMR for the conduct of pediatric studies in acute migraine with the understanding that these studies will not be necessary once the pediatric exclusivity for Maxalt expires.

2.6 Other Relevant Background Information

None submitted and none required.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the submission was acceptable. The NDA was submitted in eCTD format and conformed to CDISC SDTM standards. The information required for the review of the NDA was well-organized, easy to navigate, and complete.

3.2 Compliance with Good Clinical Practices

The applicant affirms that the study in the clinical development program was approved by ethics committees or institutional review board, in compliance with Good Clinical Practice (GCP) standards according to the International Conference of Harmonization (ICH) Guidelines and the Declaration of Helsinki, version 2004. Written informed consent was obtained for all subjects prior to any study related procedure.

The applicant certifies it did not use the services of any investigators debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

3.3 Financial Disclosures

The applicant provided required information regarding financial disclosure and there was no evidence that any study investigators had financial arrangements that may have introduced significant bias into the results of this trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review found deficiencies in the following categories: process description, drug formulation, impurities, drug product specification, container closure, stability, and environmental impact assessment. It was also determined that the CMC deficiencies precluded discussion of labeling changes. The applicant was provided preliminary notice of the identified issues prior to a complete review of the entire application in a Discipline Review (DR) letter dated 12/12/13.

The following is an overview of the initial CMC deficiencies that were conveyed to the applicant:

Process Description Deficiencies:

(b) (4)

(b) (4)

Formulation Deficiencies:

(b) (4)

Deficiencies Regarding Impurities:

(b) (4)

12. Provide information pertaining to the characterization of impurities in the drug product (section P.5.5 of the submission).

Drug Product Specification Deficiencies:

13. Update the drug product specifications to include tests and acceptance criteria for physical characteristics of the film (e.g., flexibility, tensile strength, acceptable level of bubbles, etc) or provide justification, supported by data, for not monitoring these parameters in the finished product.

14. The proposed acceptance criterion for the disintegration is overly broad. Tighten the specification for disintegration to a limit that is justified data and patient requirements.

(b) (4)

17. The acceptance criterion for the dissolution in the drug product specification was revised to Q=(b) (4)% in 15 minutes. Update the drug product release and

stability specifications to reflect this change and provide dissolution data for the last time point on the stability samples with this method.

Container Closure Deficiencies:
18. Provide a detailed description of the drug product container closure system including manufacturers, materials of construction, specifications for materials and parts, certificates of compliance, certificates of analyses, DMF references and the corresponding letters of authorization for the DMF references.
19. Provide a description of any secondary packaging used for the drug product

Stability Deficiencies:
20. Revise the post approval stability commitment to provide for placement of the first three commercial batches of each strength on stability under long-term and accelerated conditions.
21. Your application lacks photostability data for the drug product. Provide photostability on at least one batch f the drug product as per ICH Q1A(R2) and Q1B or justification the exclusion of this data.
22. Provide dissolution data using the revised dissolution method from samples at the end of their shelf life or the latest stability time point to support your expiry (See comment 17 above).

Environmental Impact Assessment:
23. Amend your application to request a categorical exclusion from preparing an environmental impact consideration, citing the specific citation under 21 CFR 25.31.

4.2 Clinical Microbiology

This submission does not contain Clinical Microbiology or Non-clinical Pharmacology and Toxicology information, as the information in these fields remains unchanged from that in the approved NDA. The applicant cross-references the MAXALT-MLT NDA 20,865 for any relevant non-clinical information. The Division agreed at the pre-NDA meeting that this submission would not contain Module 4.

4.3 Preclinical Pharmacology/Toxicology

See above (Section 4.2).

4.4 Clinical Pharmacology

Please refer to Section 5.3 of this review for a complete discussion of the submitted bioequivalence study.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The following table provides an overview of the only clinical study submitted with the application, Study RZA-P9-688. The bioequivalence assessments as well as safety data are derived from this single study. The table below is reproduced from the applicant's submission.

Table 4 Overview of Clinical Study

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	RZA-P9-688	clin-stud-rep-rza-p9-688.pdf	To evaluate and compare the relative bioavailability and therefore the bioequivalence of a Rizatriptan Immediate Release Oral Film *versus* Rizatriptan Orally Disintegrating tablet after a single oral dose administration under fasting conditions as well as to assess the safety of Rizatriptan Immediate Release Oral Film.	Crossover, Fasting State	Immediate Release Oral Film *versus* Rizatriptan Orally Disintegrating tablet; 10 mg single dose; oral	24	Healthy Subjects	Single dose	Complete; Full

5.2 Review Strategy

Since the only study conducted for this application was a bioequivalence study, it is reviewed in the subsequent section, 5.3. Discussion of the study is presented in the following categories:

- Overview of study design
- Subject disposition, demographic and baseline characteristics
- Pharmacokinetic results

There was no review of efficacy as the study under review is a bioequivalence study. Therefore, Section 6 of this review not applicable.

Safety findings in the study are presented in Section 7, Review of Safety.

5.3 Discussion of Individual Studies/Clinical Trials: Study RZA-P9-688

Overview of Study Design

Title
Single Dose Crossover Comparative Bioavailability Study of Rizatriptan 10 mg Immediate Release Oral Film and Maxalt-MLT® 10 mg Orally Disintegrating Tablets in Fasting State in Healthy Male and Female Volunteers

Objectives
To evaluate and compare the relative bioavailability and therefore the bioequivalence of a rizatriptan immediate release oral film (Rizaport) versus rizatriptan orally disintegrating tablet (Maxalt-MLT®) after a single oral dose administration under fasting conditions as well as to assess the safety of rizatriptan immediate release oral film.

Trial Design
The study was a single center, randomized, laboratory-blinded, single dose, 2-period, 2-sequence, crossover design in healthy male and female subjects. The following investigational products were to be administered under fasting conditions:

Test: 1 x Rizatriptan 10 mg Immediate Release Oral Film
Reference: 1 x Maxalt-MLT® 10 mg Orally Disintegrating Tablet

The products were administered to 26 healthy male and female subjects according to Table 5.

Table 5 Study Sequences

	Period 1	Period 2
Sequence 1 (n= 13)	Test	Reference
Sequence 2 (n= 13)	Reference	Test

(Source: Applicant's submission; Clinical Study Report, Module 5, Table 2)

In each period, subjects arrived at the clinical site at least 10 hours before dosing. After a supervised overnight fast, a single oral dose of the assigned formulation was orally administered in the morning. Subjects were allowed to leave the clinical site after the 12-hour post-dose blood draw. The drug administrations were separated by a wash-out period of 7 calendar days.

Subjects were asked to place the tablet or film directly on their tongue, close their mouth and let the study drug completely dissolve in their mouth and then swallow their saliva. No water was provided with study drug administration.

For each subject, the buccal cavity was visually inspected 10 minutes and 1 hour after administration of the oral film for full disappearance of the film and any mucosal irritation. Subjects were also instructed to report any mucosal irritation throughout the duration of the entire study.

The schedule of events in the study is presented in Table 6.

Table 6 Schedule of Study Events

	Pre-Trial	Period 1		Wash-Out	Period 2		End of Study
Days*	-28 to 0	0	1	1-7	7	8	8
Informed Consent Form Signed **	X						
Admission to Unit		X			X		
Medical History	X						
Physical Examination	X						
Laboratory Tests	X		X				X
HIV, HBsAg and anti-HCV Tests	X						
Urine Ethanol and Drugs of Abuse Screening	X	X			X		
ECG	X		X			X	
Pregnancy Test	X	X			X		X
Vital Signs	X		X			X	
Drug Administration			X			X	
Blood Sampling			X			X	
Adverse Event Monitoring			X	X	X	X	X

* The days assigned to each period varied according to the exact wash-out determined between each period of the study.
** The last version was to be signed prior to subject's inclusion (first drug administration).
(Source: Applicant's submission; Clinical Study Report, Module 5, Table 3)

Inclusion Criteria
Male and female volunteers, non- or ex-smokers, between the ages of 18 and 40 years, with a body mass index of 18.50 to less than 30.00 kg/m_2, and body weight of at least 55 kg were included in the study. Subjects were in good health as determined by a medical history, physical examination (including vital signs), electrocardiogram (ECG) and the usual clinical laboratory tests as well as negative screening of cotinine, ethanol and drugs of abuse in urine and negative pregnancy test (for female subjects).

Pharmacokinetic Assessments
Blood samples for pharmacokinetic analyses were collected at the following time points: prior to and at 0.08, 0.17, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2, 2.25, 2.5, 2.75, 3.00, 4.00, 6.00, 8.00 and 12.00 hours after drug administration.

PK parameters for the study were C_{max}, T_{max}, AUC_T, AUC_∞, $AUC_{T/\infty}$, K_{el} and $T_{½el}$. These parameters were estimated using non-compartmental approach.

Statistical analysis based on a parametric random ANOVA model of the pharmacokinetic parameters; two-sided 90% confidence interval of the ratio of geometric means for the C_{max}, AUC_T and AUC_∞ based on ln-transformed data; T_{max} based on a non-parametric approach.

ANOVA model:
- fixed factors: sequence, period, treatment
- random factor: subject (nested within sequence)

Safety Assessments
Safety was evaluated through assessment of adverse events, standard laboratory evaluations, vital signs and ECGs. A complete review of safety findings is presented in Section 7 of this review.

Subject Disposition and Demographic Characteristics

Number of Subjects (Planned and Analyzed)
Planned for inclusion: 26
Included: 26
Drop-outs: 2
Analyzed: 24
Considered in the pharmacokinetic and statistical analysis: 24
Considered in the safety analysis: 26

Pharmacokinetic Population
Of the 26 healthy male and female subjects who were included in the study, 24 subjects completed the crossover design and received a single oral dose of the assigned formulation on day 1 and day 8 of the trial.

Of the 26 enrolled subjects, 2 subjects (Subjects # (b) (6)) were withdrawn from the study and their PK data were removed from analysis. Subject (b) (6) was withdrawn after dosing in period 2 of the study after a portion of the subject's saliva dropped on the floor (approximately 0.5 mL). Subject (b) (6) was withdrawn before dosing of period 2 due to a positive cocaine test.

Demographics of Study Population
The demographic characteristics of the subjects enrolled during the study are summarized in the table below.

Table 7 Demographic Characteristics of Subjects

Demographic Characteristic	Bioequivalence Study N=26
Sex	
Male	14 (53.8%)
Female	12 (46.2%)
Height	
Mean ± SD	171.1±8.3cm
Range	154.5 – 187.0cm
Weight	
Mean ± SD	72.8±11.4kg
Range	55.2 –95.6kg
Race	
Caucasian White	23 (88.5%)
African American	3 (11.5%)

(Source: Applicant's submission; Clinical Study Report, Module 5, Table 14.1.2)

Even though the study was conducted in the healthy volunteers, the demographics and subject characteristics noted in this study paralleled typical migraine trials, with more females than males and more whites than other races.

Pharmacokinetic Results

Twenty-four subjects were included in the pharmacokinetic and statistical analysis. The PK profiles of rizatriptan after administration of either rizatriptan oral film (Test) or Maxalt-MLT® (Reference) are shown in the table below.

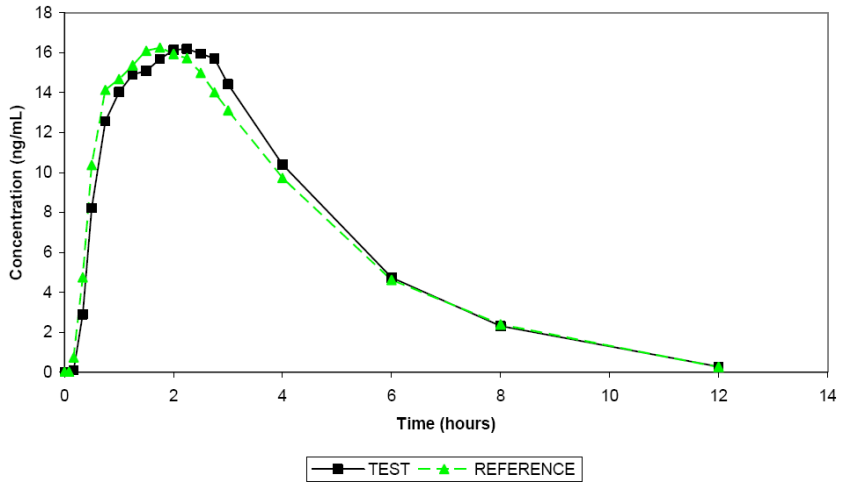
Table 8 Summary Results of Rizatriptan Pharmacokinetic Parameters

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	20.672	28.6	21.140	27.5
ln (C_{max})	2.9880	9.9	3.0110	9.9
T_{max} (hours) §	1.63	47.0	1.63	55.3
AUC_T (ng·h/mL)	75.784	23.6	74.362	21.0
ln (AUC_T)	4.3023	5.4	4.2887	4.8
AUC_∞ (ng·h/mL)	80.571	21.3	80.289	18.8
ln (AUC_∞)	4.3683	4.8	4.3694	4.2
$AUC_{T/\infty}$ (%)	95.83	2.3	94.83	2.7
K_{el} ($hours^{-1}$)	0.3859	13.9	0.3703	12.9
$T_{½el}$ (hours)	1.83	14.2	1.90	12.3

§ $T_{max,}$ the median is presented
Test = rizatriptan oral film Reference = Maxalt-MLT®
(Source: Applicant's submission; Clinical Study Report, Module 5, Table 6)

The mean measured plasma concentration versus time profile, derived from the administration of the Test and Reference products, is depicted in Figure 2. Of note, the terminal phases of rizatriptan could not be adequately estimated for 2 subjects in the study (Subjects # (b) (6) Therefore, AUC_∞, $AUC_{T/\infty}$, $T_{½el}$ and K_{el} parameters were not calculated for these subjects. The number of subjects included in the statistical analysis of these parameters was 22.

Figure 2 Linear Profile of Mean Plasma Concentration of Rizatriptan versus Time



Test = rizatriptan oral film Reference = Maxalt-MLT®
(Source: Applicant's submission; Clinical Study Report, Module 5, Figure 1)

Comparison of results with standards for bioequivalence is presented in Table 9.

Table 9 Comparative Bioavailability of Rizatriptan

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	20.0	19.845	20.308	97.72	88.57	107.82
AUC_T	8.8	73.868	72.870	101.37	97.07	105.86
AUC_∞	8.0	78.744	78.713	100.04	95.94	104.31

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞
Test = rizatriptan oral film Reference = Maxalt-MLT®
(Source: Applicant's submission; Clinical Study Report, Module 5, Table 7)

Summary Findings
The ratio and corresponding 90% confidence intervals of the relative C_{max}, AUC_∞, $AUC_{T/\infty}$ geometric LSmeans of the Test to Reference formulation are within the pre-specified 80% to 125% bioequivalence range. Both, rizatriptan oral film and Maxalt-MLT®, achieved similar T_{max}. The median T_{max} for both products was 1.63 hours.

Overall, the Clinical Pharmacology reviewer of this submission has found that the results of the PK study demonstrate that rizatriptan oral film is bioequivalent to Maxalt-MLT®.

6 Review of Efficacy

Not applicable as there was no efficacy trial conducted for rizatriptan oral film.

7 Review of Safety

Safety Summary

No new or unexpected adverse events were detected in the single bioequivalence study that formed the basis of the NDA (Study RZA-P9-688). I identified no significant deficiencies in the NDA safety submission. The applicant submitted all necessary summaries and supporting data. There were no notable inconsistencies between the data sources. The routine clinical safety testing was appropriate and capable of identifying major safety signals of rizatriptan oral film.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety data analyzed in this review was derived from Study RZA-P9-688. This was the only study submitted in the NDA.

7.1.2 Categorization of Adverse Events

The applicant defined adverse events (AEs) as “any untoward medical occurrence in a clinical investigation subject administered an investigational product and which did not necessarily have a causal relationship with this treatment. An adverse event could therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product”.

Adverse event categorization and preferred terms used in coding AEs were referenced to the Medical Dictionary for Regulatory Activities (MedDRA), version 13.1. During the review, I audited the case report forms and narratives. No systematic errors in coding were detected.

7.2 Adequacy of Safety Assessments

The adequacy of exposure as a function of both the size of the safety database and the duration of exposure was acceptable. Overall, the quality of the applicant's safety data is adequate and complete.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 26 subjects entered the study and received at least one of the investigational products. Twenty-five of the 26 subjects who entered the study received both investigational products. The demographics of the study population are discussed in Section 5.3 of this review.

7.2.2 Explorations for Dose Response

This is a 505(b)(2) application, based on bioequivalence to the referenced listed drug (Maxalt-MLT®). No new data exploring a dose response was acquired.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was conducted as part of the NDA.

7.2.4 Routine Clinical Testing

The following clinical tests were conducted in the study:

- Adverse events (AEs)
- Clinical laboratory evaluations
- Vital signs
- Electrocardiograms (ECGS)
- Physical examinations
- Use of concomitant medications
- Pregnancy testing

Additionally, the buccal cavity was visually inspected 10 minutes and 1 hour after administration of the oral film for full disappearance of the film and for any mucosal irritation. Subjects were also required to report any mucosal irritation throughout the duration of the study.

The clinical safety tests conducted in the trial were appropriate and capable of identifying major safety signals.

7.2.5 Metabolic, Clearance, and Interaction Workup

No additional data was generated for this NDA. No formal drug-drug interaction studies have been performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Please see Review Section 2.4, where the triptan class safety issues are presented. As noted, the triptans have several areas that have been identified for close monitoring in the trials. The events are:

Drug-Associated Cardiac Events and Fatalities: These have been observed both in the Premarketing Experience and Post-marketing Experience with triptans as detailed in Section 2.4. There were no fatalities in the submitted study.

Drug-Associated Cerebrovascular Events and Fatalities: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or subcutaneous triptan, and some have resulted in fatalities. No reported incidences of cerebrovascular events were documented in the applicant's trial.

Other Vasospasm-Related Events: Triptans may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported. Vital Signs were adequately monitored in the study.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome may occur with triptans, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension.

Concomitant Drug Use: In patients taking MAO-A inhibitors, sumatriptan plasma levels attained after treatment with recommended doses are nearly double those obtained under other conditions.

Use in Women of Childbearing Potential: Pregnancy tests were conducted routinely during the trials. Outcomes of the reported pregnancies in the clinical trials are discussed below in Section 7.6.2 (Human Reproduction and Pregnancy Data).

Hypersensitivity: Hypersensitivity (anaphylaxis/anaphylactoid) reactions were monitored during the study.

These events, ischemic heart disease, hepatotoxicity, hypersensitivity, cerebrovascular events, convulsive disorders, visual disturbances, and possible interactions with serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) (serotonergic syndrome) have been identified by the FDA for safety monitoring.

7.3 Major Safety Results

There were no deaths, serious adverse events, or significant adverse events reported during the trial. No additional submission safety concerns were identified during the review.

There were no discontinuations or dropouts due to an AE. Of the 26 enrolled subjects, 2 subjects (Subjects # (b) (6)) were withdrawn from the study and are discussed in Section 5.3 of this review. Reasons for their withdrawal were not related to safety issues or withdrawal of consent.

Three of the 26 subjects in the study experienced a total of 3 drug related AEs. Two subjects (8%) of the 26 subjects reported 2 AEs after the single administration of Test product, rizatriptan oral film. One subject (4%) of the 25 subjects reported 1 AEs after the single dose of administration of Reference product, Maxalt-MLT®. A total of 25 subjects were evaluated in the Reference group because one subject (Subject # (b) (6) was removed from the trial after testing positive for cocaine. That subject had already taken Test product and therefore has been included in the safety analysis for that group.

The drug related AEs occurred in the form of somnolence only. The severity of the AEs ranged from mild to moderate. No severe AEs were observed during the study. Table 10 provides a summary of the drug related AEs reported in the study.

Table 10 Subjects Who Experienced Drug Related Adverse Events Following Treatment with Rizatriptan Oral Film and Maxalt-MLT®

	Rizatriptan	
	Oral Film N=26	Maxalt-MLT® N=25
Total number of subjects with at least 1 AE	**2 (7.7%)**	**1 (4.0%)**
Nervous System Disorders	**2 (7.7%)**	**1 (4.0%)**
Somnolence	2	1

(Source: Applicant's submission; Summary of Clinical Safety, Module 2, Table 2.7.4-6)

Additionally, examination of the buccal cavity at 10 minutes and 1 hour after administration of study drug revealed no abnormalities. There were also no reports of any mucosal irritation throughout the duration of the study.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

As shown in Table 10, drug related AEs occurred in the form of somnolence only. With the exception of one abnormal lab value that was not drug related (discussed below), there were no other AEs in the study.

7.4.2 Laboratory Findings

Laboratory measurements [hematology, biochemistry (including lipid profile at screening only) and urinalysis] were assessed at screening, after the collection of the last blood sample of the first period and at study completion (post-study).

Serology (HIV, HBsAg and anti-HCV) and toxicology (cotinine, ethanol and drugs of abuse) was performed at screening. Furthermore, a serum pregnancy test was performed at screening, at female subjects' arrival, prior to each period of the study and at study completion (post-study).

Toxicology (ethanol and drugs of abuse) was performed at subjects' arrival, prior to each period of the study.

One subject (Subject # (b) (6) had an abnormal lab value of leukocyte esterase and leukocytes in the urine during period 1 and post-study. This AE was reported as not related to study drug. I have reviewed the case and concur with the applicant's assessment.

All serology and toxicology test results were negative with the exception of toxicology test results for Subject # (b) (6) whose urine tested positive for cocaine prior to dosing of period 2 and was subsequently withdrawn from the study.

7.4.3 Vital Signs

Vital signs (blood pressure, pulse rate and body temperature) were recorded at screening and prior to each drug administration. Blood pressure and pulse rate will also be recorded approximately 1, 2 and 4 hours after each drug administration.

No clinically significant on-study vital signs were recorded during this study.

7.4.4 Electrocardiograms (ECGs)

An ECG was recorded at screening and approximately 2.5 hours following each drug administration.

No clinically significant on-study ECG assessments were recorded during this study

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were submitted for this NDA.

7.5 Other Safety Explorations

Safety explorations such as dose dependency for adverse events, time dependency for adverse events, or drug-disease interactions were not conducted for this application.

7.6 Additional Safety Evaluations

Please refer to the Maxalt-MLT® Package Insert for information related to the following special groups and situations:

Human carcinogenicity
Human reproduction and pregnancy data
Pediatrics and assessment of effects on growth
Overdose, drug abuse potential, withdrawal and rebound

7.7 Additional Submissions / Safety Issues

There were no data from submissions other than those noted above.

8 Postmarket Experience

Rizaport is not approved for use and therefore there are no available postmarketing data. Postmarketing information related to rizatriptan orally disintegrating tablet can be found in the Maxalt-MLT® Package Insert.

9 Appendices

9.1 Literature Review/References

The last NDA supplement submitted by Merck for Maxalt-MLT® was filed on Dec 16th, 2011. The applicant conducted a comprehensive literature search seeking reports concerning rizatriptan that were published since that time, from January 1, 2011 through February 1, 2013. This new literature search was also cross-referenced with the newly available prescribing information on Maxalt-MLT® approved in December 2011.

The literature search found 4 papers that reported new adverse events. Review of these citations found the adverse events to be unrelated to the medication or have already been mentioned in the label. Additionally, I reviewed the literature citations submitted by the applicant for this NDA and concur with the applicant's review.

9.2 Labeling Recommendations

Recommendations regarding labeling have been deferred at this time.

9.3 Advisory Committee Meeting

No advisory committee consideration is needed for this application.

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/s/

NUSHIN F TODD
01/15/2014

NICHOLAS A KOZAUER
01/15/2014